REVIEW ARTICLE

MEDICAL PROGRESS

Febrile Urinary Tract Infections in Children

Giovanni Montini, M.D., Kjell Tullus, M.D., Ph.D., and Ian Hewitt, M.B., B.S.

From the Department of Pediatrics, Azienda Ospedaliero–Universitaria Sant'Orsola-Malpighi, Bologna, Italy (G.M.); the Department of Pediatric Nephrology, Great Ormond Street Hospital, London (K.T.); and Princess Margaret Hospital for Children, Perth, Australia (I.H.). Address reprint requests to Dr. Montini at the Department of Pediatrics, Azienda Ospedaliero–Universitaria Sant'Orsola-Malpighi, Via Massarenti 11, Padiglione 13, 40138 Bologna, Italy, or at giovanni.montini@aosp.bo.it.

N Engl J Med 2011;365:239-50.

ACUTE PYELONEPHRITIS IS THE MOST COMMON SERIOUS BACTERIAL INFECtion in childhood; many affected children, particularly infants, have severe symptoms. Most cases are readily treated, provided diagnosis is prompt, though in some children fever may take several days to abate.

Approximately 7 to 8% of girls and 2% of boys have a urinary tract infection during the first 8 years of life.[1,2] Febrile urinary tract infections have the highest incidence during the first year of life in both sexes, whereas nonfebrile urinary tract infections occur predominantly in girls older than 3 years.[2] After infancy, urinary tract infections confined to the bladder are generally accompanied by localized symptoms and are easily treated. In contrast, the presence of fever increases the probability of kidney involvement (sensitivity, 53 to 84%; specificity, 44 to 92%)[3] and is associated with an increased likelihood of underlying nephrourologic abnormalities and a greater risk of consequent renal scarring.[4]

Kidney scarring related to urinary tract infection has been considered a cause of substantial long-term morbidity.[5] Thus, children with proven infections have been intensively evaluated and treated, and they have often undergone surgery or have received long-term antibiotic prophylaxis.[3,6] Such approaches have been questioned.[7,8] A number of trials have been conducted or are under way to determine optimal approaches to the assessment and management of initial febrile urinary tract infections and subsequent interventions for them. This review summarizes the diverse views on this controversial topic.

BACKGROUND

Antibiotic treatment of children with febrile urinary tract infections has almost eliminated the risk of death, which was approximately 20% among children hospitalized for acute pyelonephritis in the early 20th century.[9] Some 50 years ago, one study described renal parenchymal injury in 210 of 597 children treated for recurrent urinary tract infections.[10] Another study in that era reported on an 11-to-27-year follow-up of 72 children hospitalized for urinary tract infections; 18% had died, 8% had progressive renal insufficiency, and 22% had persistent untreated or recurrent infection.[11] Both studies assumed that kidney damage was related solely to urinary tract infection, overlooking the possibility that congenital renal abnormalities contributed to these outcomes. In the early 1970s, the evolving concept of reflux nephropathy linked vesicoureteral reflux to pyelonephritis and late renal scarring.[12] Consequently, children who had had febrile urinary tract infections were routinely evaluated for urinary tract abnormalities and often received long-term antibiotic prophylaxis[10,13]; surgical correction of vesicoureteral reflux became standard care.[14]

In the 1980s, two randomized, controlled trials comparing antibiotic prophylaxis alone with surgical correction alone or in combination with adjuvant prophylaxis had similar results in the medical and surgical groups.[15,16] One of these studies showed a high prevalence of scarring (38%) before treatment commenced, whereas rates of new scarring and progression of existing scarring were low (2% and 9%, respectively) and were unrelated to persistent reflux or breakthrough infections.[15] Such results highlight an important issue: the distinction between primary renal damage that precedes infection and scars related to urinary tract infection. Primary renal damage is linked to prior obstruction, genetic and developmental factors that result in maldevelopment (hypodysplasia) of the urinary tract, or both. However, inflammatory processes (pyelonephritis) that occur in the context of infection may also produce scars.

Improved antenatal ultrasonographic techniques have resulted in frequent recognition of kidney and urinary tract abnormalities in utero. By the mid-1980s, major renal defects[17] and hypodysplastic kidneys, which are often accompanied by vesicoureteral reflux, could be identified before birth.[18-20] Now, in contrast to earlier studies[5] that suggested that acquired pyelonephritis-associated damage was the most common cause of chronic kidney disease in children, adequate antenatal ultrasonographic studies show that intrinsic disease was probably involved. Population-based studies in the present era, in which prenatal ultrasonographic studies are common, identify increasing numbers of children with congenital renal anomalies and reflux.[21-24]

LONG-TERM CONSEQUENCES

Approximately 60% of children with febrile urinary tract infections, if evaluated during or just after the infection, have visible photon defects on renal scintigraphic studies with technetium-99m–labeled dimercaptosuccinic acid (DMSA) — findings considered evidence of parenchymal localization (pyelonephritis). Of these, 10 to 40% will have permanent renal scarring,[4,25] unrelated to age.[26,27] The long-term medical risks of infection-related scarring in previously healthy kidneys are incompletely understood. Few population-based, follow-up studies have been performed.[28,29] A Swedish study[28] followed 57 children with nonobstructive renal scarring and 51 matched subjects without renal scarring at urographic examination, 16 to 26 years after a first symptomatic urinary tract infection. Children with unilateral scars and those without scars had similar glomerular filtration rates at the end of follow-up; however, the median glomerular filtration rate in seven children with bilateral scars decreased from 94 ml per minute per 1.73 m^2 of body-surface area to 84 ml per minute per 1.73 m^2. No difference in ambulatory 24-hour blood pressure was found between children with scars and those without scars.[29]

The few prospective studies that have been performed showed a low rate of long-term consequences. In the International Reflux Study in Children, hypertension was reported in 4 of 252 patients (1.6%) with reflux, mainly grade IV, prospectively followed for 10 years.[30] (The classification of vesicoureteral reflux is explained in Fig. 1.) One of the 133 children whose glomerular filtration rate was measured had a clearance that had fallen below the minimal study entry level of 70 ml per minute per 1.73 m^2.[30] Most of the prospective studies are limited by relatively short follow-up.[30,31]

In contrast, retrospective studies have suggested that renal scarring related to urinary tract infection carries a clinically significant risk, with high subsequent rates of chronic kidney disease (up to 20%), hypertension (20 to 40%), and preeclampsia (10 to 20%).[32-34] Such retrospective studies are limited by referral bias in that specialized centers may not see the vast majority of children, who have uncomplicated febrile urinary tract infections. In addition, some retrospective studies recruited patients before the widespread availability of prenatal ultrasonographic screening.[32-34] Furthermore, other studies assumed that all patients with chronic kidney disease and vesicoureteral reflux had had undocumented urinary tract infections in the past.[32-34]

Registries[19,21,35] of children with end-stage renal disease or with transplants generally list primary renal diseases. The North American Pediatric Renal Trials and Collaborative Studies[21] list primary diagnoses for 9854 children who had received transplants over the previous 20 years — 16% had hypodysplasia, 16% obstructive uropathy, and 5% reflux nephropathy. These data highlight the recognition of congenital damage as a cause of chronic kidney disease. However, such registries do not specifically address febrile urinary

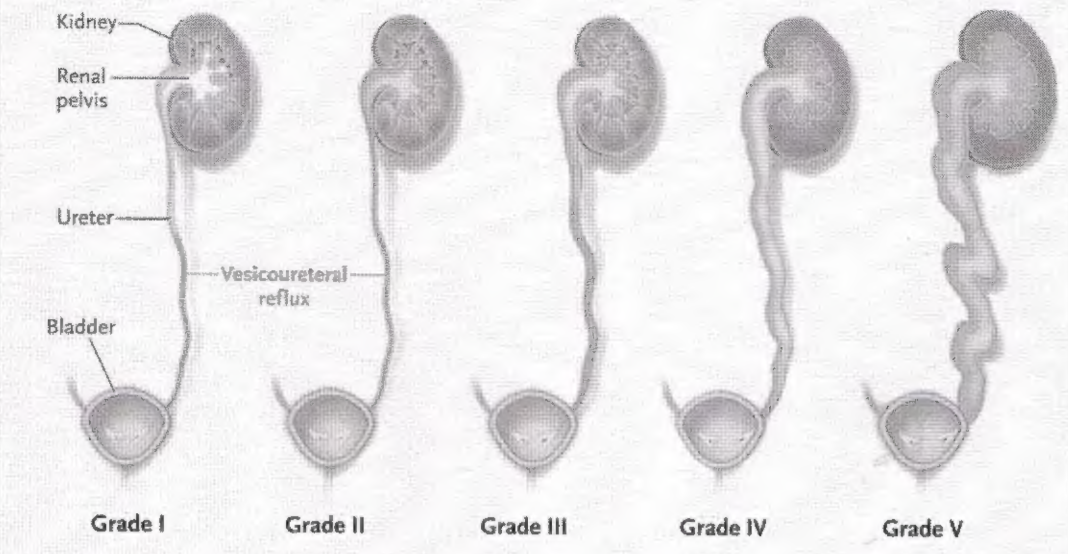

Figure 1. **International Classification of Vesicoureteral Reflux.**

This classification grades vesicoureteral reflux as follows: grade I, reflux into a nondilated ureter only; grade II, reflux into the renal pelvis and calyces without dilatation; grade III, reflux into a mildly to moderately dilated ureter and renal pelvis with no or only slight blunting of fornices; grade IV, moderate dilatation and tortuosity of the ureter and renal pelvis, with obliteration of the sharp angle of the fornices but maintenance of papillary impressions in most calyces; and grade V, gross dilatation and tortuosity of the ureter, renal pelvis, and calyces with loss of papillary impressions.[16]

tract infections as a risk factor for chronic kidney disease, and the data on primary diseases are retrospective and are not diagnostically uniform.

PATHOPHYSIOLOGY OF PYELONEPHRITIS AND SCAR FORMATION

The kidneys and the urinary tract are usually germ-free. When bacteria enter, a number of conditions may develop. Some children will have asymptomatic bacteriuria and some cystitis with inflammation, mainly in the bladder mucosa, but a few children will have febrile urinary tract infections, with systemic activation of the inflammatory process.[9]

Most children with primary immunodeficiency diseases do not appear to be prone to urinary tract infections. Even children with primary antibody-deficiency states, who have frequent bacterial infections,[36] as well as those with severe combined immunodeficiency syndromes affecting both T-cell and B-cell function, have few urinary tract infections. When urinary tract infections develop in such children, associated renal tract abnormalities usually appear to play a role,[37,38] indicating that adequate urine flow and intact uroepithelium are key in the prevention of urinary tract infections.

Certain bacteria have characteristics that favor the establishment of infection. For example, *Escherichia coli* bacteria have P fimbriae that facilitate uroepithelial attachment, even in the presence of adequate urine flow.[39] In children with kidney malformations, who may have abnormal urinary flow, residual urine after voiding, or both, even nonattaching bacteria may cause infection.[40]

When bacteria invade the kidney, localized inflammation develops, triggering the innate immune system through multiple pathways. It is well recognized that toll-like–receptor signaling after recognition of bacteria[41] initiates an immune response involving nuclear factor κB and the production of cytokines and chemokines[42,43] (Fig. 2). If a renal parenchymal infection is limited in extent and duration, full recovery can occur. However, continued inflammation may lead to scarring, though predisposing factors are not well understood. Although polymorphisms in vascular endothelial growth factor and transforming growth factor β1,[44] as well as ethnic group,[45] have been proposed as risk factors for renal scar-

ring, studies are inconclusive and lack validation sets.

An improved understanding of the pathogenesis of renal scarring related to urinary tract infection would logically lead to the development of adjunctive treatment strategies. Studies in animal models[46] have shown that glucocorticoids inhibit infection-related renal scarring. One study involving children with acute pyelonephritis[47] showed that dexamethasone significantly decreased urinary levels of interleukin-6 and interleukin-8, suggesting a possible role for glucocorticoids in the prevention of scar formation. However, definitive studies are lacking.

TREATMENT OF AN ACUTE EPISODE

Antibiotic treatment is the cornerstone of treatment for acute urinary tract infections and is important for preventing parenchymal localization of the infection.[48] Until the mid-1990s, there was little agreement regarding the choices of antibiotic, mode of administration, and duration of therapy.[49] Between 1995 and 2001, four studies compared longer courses (7 to 14 days) of intravenous antibiotic therapy with shorter courses (3 to 4 days) followed by oral treatment.[50-53] A systematic review of these studies showed no difference in rates of subsequent renal damage, irrespective of the duration of intravenous therapy.[49] In a 1999 study, Hoberman et al.[25] compared 3 days of intravenous cefotaxime followed by 11 days of oral cefixime with 14 days of oral cefixime alone in 306 children 1 to 24 months of age; there was no difference in outcome. A more recent study involving 502 children 1 month to younger than 7 years of age had similar results.[54] In both studies,[25,54] treatment was administered after a first febrile urinary tract infection. Thus, it appears that oral antibiotics may be appropriate in children older than 1 month of age who have had a first febrile urinary tract infection.

The American Academy of Pediatrics[3] currently recommends that parenteral antibiotic therapy and hospitalization be considered for children who appear to be severely ill or dehydrated or who are unable to retain oral intake. The organization suggests considering outpatient parenteral antibiotics when a child is vomiting but does not appear "toxic," or when nonadherence is a concern.[3] The choice of antibiotics depends on resistance patterns in a given institution or region. Cephalosporins and amoxicillin–clavulanic acid are the oral antibiotics most often used.[3,7] When intravenous treatment is required, no particular antibiotic has been shown to be superior[7]; cephalosporins and aminoglycosides are frequently recommended.[3,7] Table 1 lists antibiotics commonly used for febrile urinary tract infections.

INTERVENTIONS AFTER URINARY TRACT INFECTION

ANTIBIOTIC PROPHYLAXIS

Antibiotic prophylaxis was first used empirically in the 1950s,[10] but the first controlled trials of prophylaxis did not occur until the late 1960s. Three small studies[56-58] compared prophylaxis with placebo or no treatment; results were inconclusive.[59]

Between 2006 and 2010, six prospective, randomized, controlled trials that compared prophylaxis with no therapy were published. Important in considering these studies is the degree of vesicoureteral reflux (Fig. 1). Four studies involved a total of 899 children assigned to prophylaxis or no prophylaxis for 12 to 24 months; most did not have vesicoureteral reflux or had reflux up to grade III.[60-63] All four studies[60-63] showed that the rates of recurrent, symptomatic urinary tract infections were similar in the two groups,[64] and two of the studies showed that grade III reflux was associated with a trend toward an increased likelihood of recurrent urinary tract infections in the no-prophylaxis groups; however, the studies were insufficiently powered for an analysis according to the grade of reflux.[61,63] In two of the four studies, scarring from recurrent pyelonephritis occurred during follow-up in 1.4 to 5.9% of the randomized population.[60,63] All four studies[60-63] were underpowered and unblinded. Furthermore, the results cannot be generalized to children with grade III to V reflux.

The Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal Tracts study (PRIVENT; Australian New Zealand Clinical Trials Registry number, ACTRN12608000470392),[65] in which 576 children were randomly assigned to receive prophylaxis or placebo for 12 months, addressed many shortcomings inherent in earlier trials. The primary

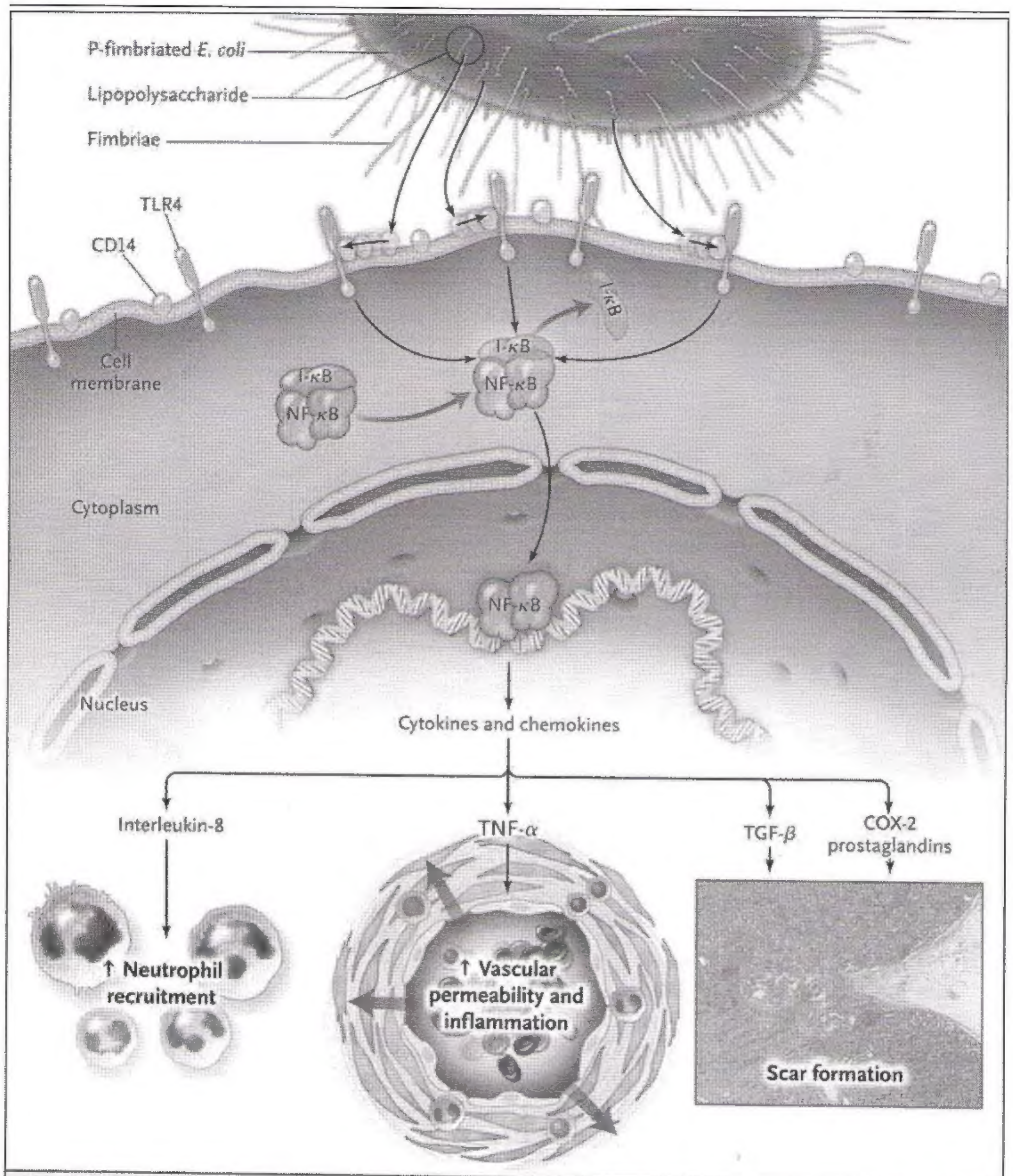

Figure 2. Pathophysiology of Acute Pyelonephritis.

Acute pyelonephritis occurs when bacteria ascend to the kidneys, causing intrarenal infection. *Escherichia coli* bacteria with P fimbriae attach to uroepithelial cells and cannot be flushed out. The endotoxin (lipopolysaccharide) of the bacteria binds to CD14 on the cell surface, activating toll-like receptor (TLR) 4. Through subsequent steps, this activates transcription factor nuclear factor κB (NF-κB), which migrates into the cell nucleus, stimulating production of inflammatory factors, including cytokines, chemokines, nitric oxide, and transforming growth factor β. These mediators induce an inflammatory response, which increases vascular permeability and recruitment of neutrophils to resolve the infection, but the mediators are also responsible in part for the ensuing kidney scarring. COX-2 denotes cyclooxygenase-2, I-κB inhibitory protein κB, TGF-β transforming growth factor β, and TNF-α tumor necrosis factor α.

Table 1. **Antibiotic Treatment of Febrile Urinary Tract Infection.***

Treatment	Dose	Comments
Intravenous		
Cephalosporins		Increasing resistance
Cefotaxime	12.5–45 mg per kg of body weight four times per day	
Ceftazidime	30–50 mg per kg three times per day	Good coverage for pseudomonas
Ceftriaxone	50–75 mg per kg once daily or 25–37.5 mg per kg twice per day	Advantage of once-daily dosing; contraindicated in neonates, especially premature infants
Aminoglycosides		Useful for patients with cephalosporin allergy; nephrotoxic; serum levels must be monitored and dosage adjusted accordingly; single daily dosage supported by meta-analysis[55]
Gentamicin	2–2.5 mg per kg three times per day	
Amikacin	7.5 mg per kg twice per day	
Piperacillin–tazobactam	2–9 months of age: 80 mg of piperacillin and 10 mg of tazobactam per kg three times per day; more than 9 months of age: 100 mg of piperacillin and 12.5 mg of tazobactam per kg three times per day	Broad spectrum of bactericidal activity
Oral		
Trimethoprim–sulfamethoxazole	4 mg per kg twice per day (dose expressed in trimethoprim-equivalent units)	High resistance rates; risk of allergic reaction
Amoxicillin–clavulanic acid	45 mg per kg twice per day (dose expressed in amoxicillin-equivalent units)	Increasing resistance
Cephalosporins		Increasing resistance
Ceftibuten	9 mg per kg once daily	
Cefixime	8 mg per kg once daily	
Ciprofloxacin	10–20 mg per kg twice per day	A second choice for the treatment of complicated urinary tract infections; increasing resistance; increased risk of musculoskeletal adverse events

* Dosages are in accordance with product monographs approved by the Food and Drug Administration and compiled by the drug manufacturers. The monographs are available at www.drugs.com. The doses listed may vary from those used at some institutions and in some clinical trials; always consult current product monographs, with particular attention to the maximum recommended dose.

outcome was a symptomatic urinary tract infection. Recurrent urinary tract infection was diagnosed in 13% of the antibiotic group and 19% of the placebo group, and significant between-group differences were seen for both symptomatic and febrile urinary tract infections. The authors state that at 12 months, prophylaxis would have been required in 14 patients (95% confidence interval [CI], 9 to 86) to prevent one urinary tract infection. However, 17% of the study participants were not evaluated for reflux, and 49% of those who were did not have reflux. Furthermore, there was inadequate power to evaluate children according to the grade of reflux. Thus, as acknowledged by the authors,[65] the benefit of prophylaxis in preventing kidney damage remains speculative, given the modest reduction in the risk of urinary tract infection and low risk of damage after a single infection.

In the recent Swedish Reflux Trial,[66] 203 children (128 girls) 1 year of age with grade III or IV reflux were randomly assigned to one of three approaches — antibiotic prophylaxis, endoscopic correction of reflux, or surveillance — and followed for 24 months. There was a high rate of recurrent febrile urinary tract infections among girls (with 67 such infections) but not among boys (8 infections). Girls who received antibiotic prophylaxis and those who received endoscopic treatment had lower recurrence rates (19% and 23%, respectively) than those in the surveillance group (57%, P<0.001). New scarring was noted in 2 boys and 13 girls. Of the girls with new scars, 8 were undergoing surveillance and 5 had undergone en-

doscopic correction; none of the girls in the prophylaxis group had scarring (P=0.02).[67] Although the target number of 300 children was not achieved,[68] the Swedish Reflux Trial supports a role for prophylaxis in girls younger than 4 years old with grade III or IV reflux.[69]

On the basis of the studies reviewed here, we would suggest that the role of prophylaxis is questionable in children with no reflux or with grade I or II reflux, given a recurrence rate for infection of 3 to 8% per year without prophylaxis.[64] For children with grade III to V reflux, who have a much higher rate of reinfection (28 to 37%),[64,66] prophylaxis would seem appropriate, particularly in girls. There are no data on the optimal duration of prophylaxis; in most prospective trials, the treatment period has been 1 to 2 years. A recent meta-analysis of 11 trials involving 2046 patients did not support the use of prophylactic antibiotics.[70] That meta-analysis did not include subgroup analysis according to grade of reflux. Studies that evaluate children according to the severity of reflux would be useful.

A North American initiative, the Randomized Intervention for Children with Vesicoureteral Reflux study (RIVUR; ClinicalTrials.gov number, NCT00405704), which is enrolling 600 children 2 to 72 months of age with grade I to IV vesicoureteral reflux after an index febrile or symptomatic urinary tract infection, will probably provide valuable information.[71]

SURGICAL CORRECTION OF VESICOURETERAL REFLUX

Vesicoureteral reflux can be corrected by surgical reimplantation of the ureter or endoscopic injection of a bulking agent next to the vesicoureteral junction. The reported resolution rate is 98.1% for open surgery (95% CI, 95.1 to 99.1) and 83.0% for endoscopic therapy (95% CI, 69.1 to 91.4) after a single injection.[72] Data are limited concerning the durability of endoscopic treatment. The guidelines of the American Urological Association[72] recommend continuous antibiotic prophylaxis rather than surgery for nearly all infants with vesicoureteral reflux. For children older than 1 year of age, the guidelines do not recommend surgical intervention routinely but strongly favor surgery for children with higher reflux grades and the presence of scarring. According to these guidelines, antireflux procedures should be considered for breakthrough febrile urinary tract infections or recurrent infections in children receiving prophylaxis, in whom progressive scarring may occur.

ADJUNCTIVE TREATMENTS

Cranberry juice, considered to inhibit bacterial adhesion to uroepithelial cells, has been used for the prevention of recurrent urinary tract infections.[73] A Cochrane review showed that ingestion of cranberry products may decrease the number of symptomatic urinary tract infections in women[74]; a recent study suggested similar results in children.[75] However, standardization of cranberry products is lacking, which makes it difficult to compare study findings.

Circumcision has been shown to be associated with a reduced risk of urinary tract infection (P<0.001).[76,77] A meta-analysis showed that the number of circumcisions that would need to be performed to prevent one urinary tract infection was 111 in the general population. The authors suggested that circumcision would provide a net clinical benefit only in boys at high risk for urinary tract infection or in those with high-grade reflux.[77]

IMAGING AFTER A FIRST FEBRILE URINARY TRACT INFECTION

The best approach to evaluating a child after a first febrile urinary tract infection remains a contentious issue. Ultrasonography, voiding cystourethrography, and renal scintigraphy with technetium-99m–labeled DMSA have been the core imaging methods. The reason for imaging is to detect obstructive malformations, vesicoureteral reflux, and kidney damage, yet consensus on the malformations, grade of reflux, and degree of damage that are important to detect is lacking. Concerns about cystourethrography include the radiation burden (albeit small), the associated pain and distress, and the cost.

ULTRASONOGRAPHY

Ultrasonography is noninvasive and can reveal a variety of anatomical abnormalities. Ultrasonography alone detects vesicoureteral reflux only indirectly. The rate of ultrasonographic detection of grade III to V reflux varies in studies, ranging from 22%, when only dilatation of the urinary tract is defined as abnormal,[78] to 67%[79] and 86%,[80] when other ultrasonographic abnormalities (renal hypodysplasia, thickened bladder or pelvis wall, or

signs of pyelonephritis) are included. However, this imaging technique does not reliably detect low-grade reflux, pyelonephritis, or scarring.[78] In three trials involving a total of 864 children, prospective ultrasonography after an initial febrile urinary tract infection failed to reliably detect changes associated with reflux or subsequent renal damage.[78,81,82] Predominantly minor abnormalities were found in 12%,[78] 14%,[81] and 13%[82] of cases and had little influence on subsequent management. A systematic review and a more recent study indicated that approximately 70% of renal and urinary tract anomalies are detected antenatally by means of routine ultrasonography performed during the second and third trimesters of pregnancy.[83,84]

Given the low rate of detection of clinically significant abnormalities, one approach after an uncomplicated first febrile urinary tract infection in a child under 3 years of age is to ascertain whether a reliable, normal ultrasonographic study performed during the third trimester of pregnancy is available for review. If not, ultrasonography could be performed. If the course of a urinary tract infection is atypical (infection with an organism other than *E. coli*, a delayed response to appropriate antibiotics, the presence of an abnormal urinary stream, recurrent infection, or evidence of renal functional impairment[7]), ultrasonography is indicated, in our view. An alternative approach is to perform an ultrasonographic examination of the urinary tract in all children under 2 years of age after an initial febrile urinary tract infection.[3]

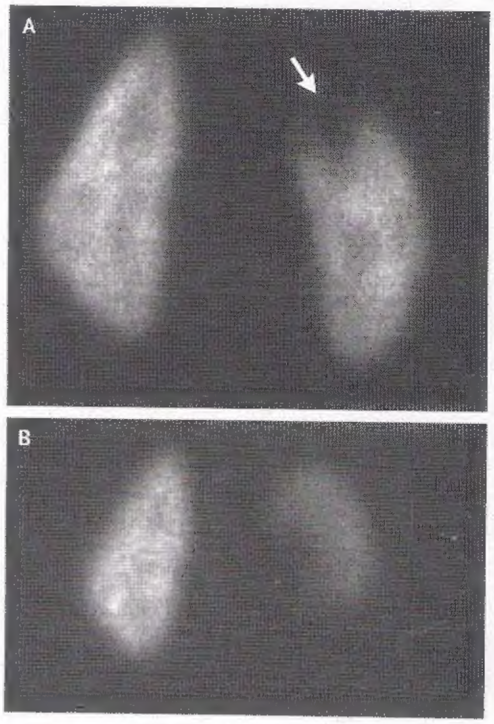

Figure 3. **Renal Scintigraphy with Technetium-99m–Labeled Dimercaptosuccinic Acid.**

Panel A shows a right kidney with a scar (arrow) related to urinary tract infection. Panel B shows a right hypodysplastic kidney, without evidence of focal scarring. Scintigraphic images courtesy of Dr. Pietro Zucchetta, Nuclear Medicine Department, University of Padua, Padua, Italy.

VOIDING CYSTOURETHROGRAPHY

Voiding cystourethrography generally necessitates instillation of a radiopaque, radioactive, or echocontrast[85] medium into the bladder through urethral catheterization, followed by serial imaging during filling and voiding to determine whether there is vesicoureteral reflux. Most controversy regarding imaging centers on this study. Advocates cite a strong association between the severity of reflux and the presence of renal damage.[86] Most would agree that detecting reflux with associated dilatation remains important, given an increased risk of renal scarring and the ability to intervene medically or surgically in such a situation.[66] Because the presence and severity of reflux can be reliably determined only by means of voiding cystourethrography, some advocate performing cystourethrography in all children after a first febrile urinary tract infection.[78,87] Others[7] argue that detection of lower grades of reflux is not essential and support a more selective approach, aimed at detection of higher grades of reflux. This latter approach suggests performing voiding cystourethrography if a child has a first febrile urinary tract infection with atypical features — such as abnormalities on antenatal or postnatal ultrasonographic examination, infection with non–*E. coli* organisms, abnormal urine stream, or evident renal dysplasia or renal insufficiency — or if a child with a repeat febrile urinary tract infection did not undergo a voiding study after the initial episode. This selective approach reduces the cost and distress associated with the procedure in children with an uncomplicated first febrile urinary tract infection who are otherwise well. However, the selective approach may miss a number of chil-

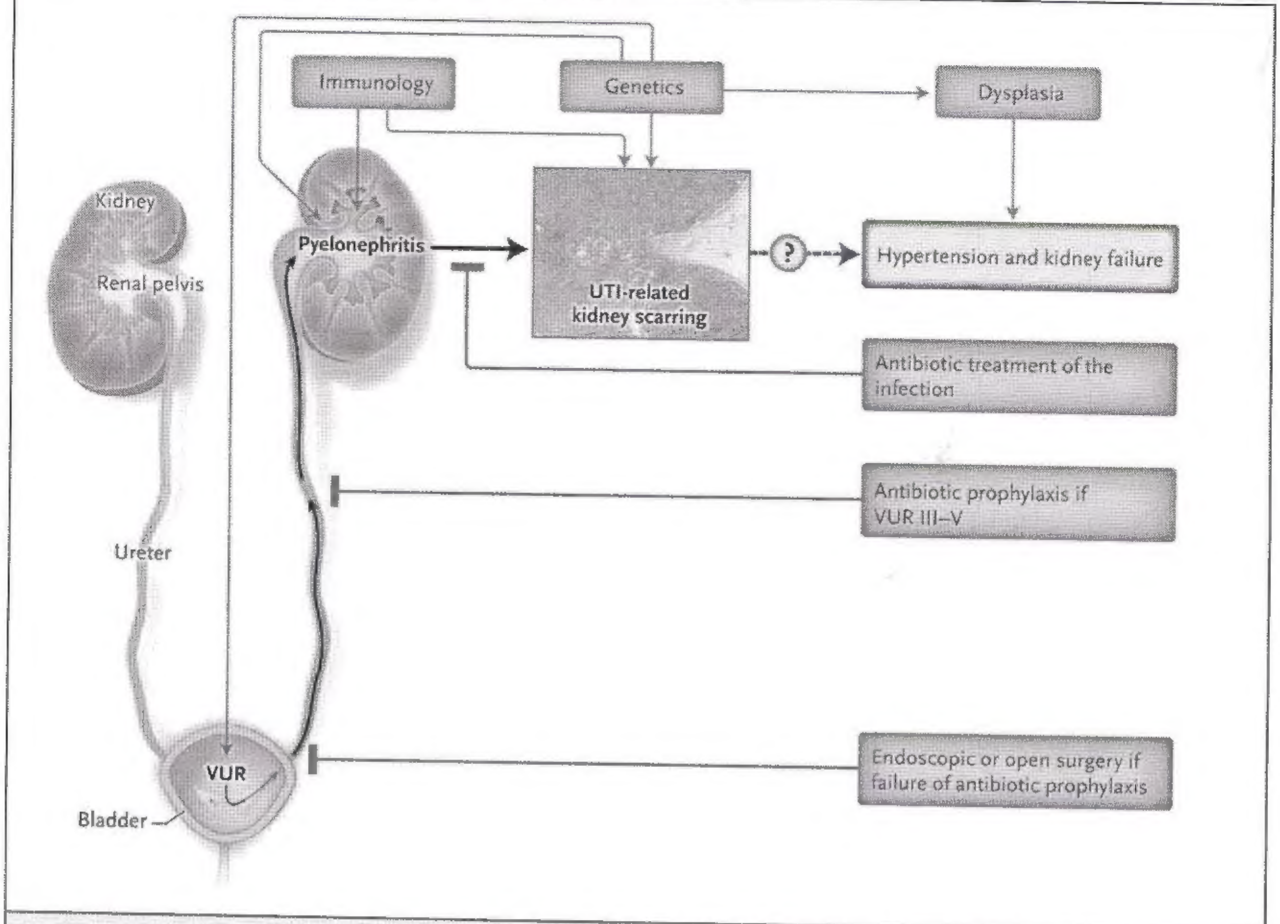

Figure 4. Current Understanding of Febrile Urinary Tract Infections and Renal Scarring.
The figure shows the current approach (blue) to febrile urinary tract infection (UTI) in children and highlights the contribution of congenital damage and the importance of immunologic and genetic factors (red). The figure also recognizes the role of infection-related kidney scarring in producing major long-term medical sequelae. Genetic factors influence both the occurrence of dysplasia and the propensity for scar formation. VUR denotes vesicoureteral reflux, and VUR III–V grade III to grade V reflux. The role of antibiotic prophylaxis that is depicted here represents our view.

dren who have clinically important reflux until another infection occurs.[7,88]

RENAL SCINTIGRAPHY

Renal scintigraphy with DMSA requires the intravenous administration of a radioactive isotope, which is then taken up by the renal parenchyma, permitting the identification of regions of decreased uptake that may represent acute inflammation (as seen in pyelonephritis) or renal scarring. No general anesthesia is required, although a light sedation by means of oral medication is indicated in rare instances. The radiation dose, approximately 1 mSv, is a concern.[89,90] This technique can be used in the acute phase of a urinary tract infection to confirm pyelonephritis, or from 6 to 12 months later to determine whether scarring has occurred. The technique may also detect the presence of renal hypodysplasia.[82,88] Differentiating renal hypodysplasia from scars related to urinary tract infection is sometimes difficult. A small kidney with uniform uptake of isotope is likely to represent congenital hypodysplasia, whereas a focal area of reduced cortical uptake associated with loss of contours, or the presence of cortical thinning, is likely to represent an infection-related scar[78] (Fig. 3).

Renal scintigraphy performed during the acute phase of a urinary tract infection, followed by cystourethrography if the scintigraphic examina-

tion suggests pyelonephritis (once a urine culture is negative), has been referred to as the "top down" approach[91,92] and focuses on putative pyelonephritis and scarring. This approach may decrease the number of cystourethrographic examinations performed. Some studies have shown a strong correlation between clinically relevant vesicoureteral reflux with dilatation and abnormal scintigraphic scans,[91,92] though a recent study[93] showed that 30.5% of 46 children with grade III to V reflux had a normal scan during an acute infection.

Some investigators recommend renal scintigraphy 6 to 12 months after an acute infection to detect the formation of scarring, which would require follow-up.[82,88]

Other imaging techniques, such as computed tomography and magnetic resonance imaging, may have a role when intrarenal abscesses are suspected or when there is a delayed response to antibiotic treatment[94] (see a recent review of imaging methods for further information[95]).

Most children with an uncomplicated first febrile urinary tract infection have an uneventful recovery. Nevertheless, there remains a lingering concern that if investigations are abandoned, one could miss the few cases in which clinically important urologic or renal problems were not detected with antenatal ultrasonography.

CONCLUSIONS

The management of febrile urinary tract infections in children is changing. Oral and intravenous antibiotics appear to be equally effective in most children. Improved prenatal ultrasonography has revealed that major kidney damage in children is frequently related to the presence of hypodysplasia, associated with urologic abnormalities (Fig. 4). However, infection-related renal scarring develops in some children; this causes further damage in dysplastic kidneys, with the potential for late effects in previously normal kidneys. The value of antibiotic prophylaxis has been questioned in recent studies (Fig. 4). Further data are needed to determine which children might benefit from antibiotic prophylaxis. Studies in progress may help to answer these questions.

Dr. Montini reports that his prior institution, Azienda Ospedaliera di Padova, has received grant support from AstraZeneca. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Hellström A, Hanson E, Hansson S, Hjälmås K, Jodal U. Association between urinary symptoms at 7 years old and previous urinary tract infection. Arch Dis Child 1991;66:232-4.

2. Mårild S, Jodal U. Incidence rate of first-time symptomatic urinary tract infection in children under 6 years of age. Acta Paediatr 1998;87:549-52.

3. American Academy of Pediatrics, Committee on Quality Improvement, Subcommittee on Urinary Tract Infection. The diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. Pediatrics 1999;103:843-52. [Errata, Pediatrics 1999;103:1052, 104:118, 2000;105:141.]

4. Jakobsson B, Svensson L. Transient pyelonephritic changes on 99mTechnetium-dimercaptosuccinic acid scan for at least five months after infection. Acta Paediatr 1997;86:803-7.

5. Pistor K, Schärer K, Olbing H, Tamminen-Möbius T. Children with chronic renal failure in the Federal Republic of Germany. II. Primary renal diseases, age and intervals from early renal failure to renal death: Arbeitsgemeinschaft fur Padiatrische Nephrologie. Clin Nephrol 1985;23:278-84.

6. Guidelines for the management of acute urinary tract infection in childhood: report of a working group of the Research Unit, Royal College of Physicians. J R Coll Physicians Lond 1991;25:36-42.

7. National Institute for Health and Clinical Excellence. Urinary tract infection in children: diagnosis, treatment and long-term management. 2007. (http://www.nice.org.uk/nicemedia/pdf/CG54fullguideline.pdf.)

8. Royal Children's Hospital Melbourne. Clinical practice guidelines. (http://www.rch.org.au/clinicalguide/cpg.cfm?doc_id=5241.)

9. Hansson S, Jodal U. Urinary tract infection. In: Avner ED, Harmon WE, Niaudet P, eds. Pediatric nephrology. 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2004:1007-26.

10. Deluca FG, Fisher JH, Swenson O. Review of recurrent urinary-tract infections in infancy and early childhood. N Engl J Med 1963;268:75-7.

11. Steele RE Jr, Leadbetter GW Jr, Crawford JD. Prognosis of childhood urinary-tract infection: the current status of patients hospitalized between 1940 and 1950. N Engl J Med 1963;269:883-9.

12. Bailey RR. The relationship of vesicoureteric reflux to urinary tract infection and chronic pyelonephritis-reflux nephropathy. Clin Nephrol 1973;1:132-41.

13. Normand IC, Smellie JM. Prolonged maintenance chemotherapy in the management of urinary infection in childhood. Br Med J 1965;1:1023-6.

14. Politano VA, Leadbetter WF. An operative technique for the correction of vesicoureteral reflux. J Urol 1958;79:932-41.

15. Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux: two years' observation in 96 children. Br Med J (Clin Res Ed) 1983;287:171-4.

16. Medical versus surgical treatment of primary vesicoureteral reflux: report of the International Reflux Study Committee. Pediatrics 1981;67:392-400.

17. Romero R, Cullen M, Grannum P, et al. Antenatal diagnosis of renal anomalies with ultrasound. III. Bilateral renal agenesis. Am J Obstet Gynecol 1985;151:38-43.

18. Marra G, Oppezzo C, Ardissino G, et al. Severe vesicoureteral reflux and chronic renal failure: a condition peculiar to male gender? Data from the ItalKid Project. J Pediatr 2004;144:677-81.

19. Ardissino G, Daccò V, Testa S, et al. Epidemiology of chronic renal failure in

children: data from the ItalKid project. Pediatrics 2003;111(4):e382-e387.
20. Reuss A, Wladimiroff JW, Niermeijer MF. Antenatal diagnosis of renal tract anomalies by ultrasound. Pediatr Nephrol 1987;1:546-52.
21. North American Pediatric Renal Trials and Collaborative Studies. Annual report, 2008. (https://web.emmes.com/study/ped.)
22. Wennerström M, Hansson S, Jodal U, Stokland E. Primary and acquired renal scarring in boys and girls with urinary tract infection. J Pediatr 2000;136:30-4.
23. Broyer M, Chantler C, Donckerwolcke R, Ehrich JH, Rizzoni G, Schärer K. The paediatric registry of the European Dialysis and Transplant Association: 20 years' experience. Pediatr Nephrol 1993;7:758-68.
24. Esbjörner E, Berg U, Hansson S. Epidemiology of chronic renal failure in children: a report from Sweden 1986-1994. Pediatr Nephrol 1997;11:438-42.
25. Hoberman A, Wald ER, Hickey RW, et al. Oral versus initial intravenous therapy for urinary tract infections in young febrile children. Pediatrics 1999;104:79-86.
26. Benador D, Benador N, Slosman D, Mermillod B, Girardin E. Are younger children at highest risk of renal sequelae after pyelonephritis? Lancet 1997;349:17-9.
27. Hewitt IK, Zucchetta P, Rigon L, et al. Early treatment of acute pyelonephritis in children fails to reduce renal scarring: data from the Italian Renal Infection Study Trials. Pediatrics 2008;122:486-90.
28. Wennerström M, Hansson S, Jodal U, Sixt R, Stokland E. Renal function 16 to 26 years after the first urinary tract infection in childhood. Arch Pediatr Adolesc Med 2000;154:339-45.
29. Wennerström M, Hansson S, Hedner T, Himmelmann A, Jodal U. Ambulatory blood pressure 16-26 years after the first urinary tract infection in childhood. J Hypertens 2000;18:485-91.
30. Jodal U, Smellie JM, Lax H, Hoyer PF. Ten-year results of randomized treatment of children with severe vesicoureteral reflux: final report of the International Reflux Study in Children. Pediatr Nephrol 2006;21:785-92.
31. Smellie JM, Barratt TM, Chantler C, et al. Medical versus surgical treatment in children with severe bilateral vesicoureteric reflux and bilateral nephropathy: a randomised trial. Lancet 2001;357:1329-33.
32. el-Khatib M, Packham DK, Becker GJ, Kincaid-Smith P. Pregnancy-related complications in women with reflux nephropathy. Clin Nephrol 1994;41:50-5.
33. Zhang Y, Bailey R. A long term follow up of adults with reflux nephropathy. N Z Med J 1995;108:142-4.
34. Jacobson SH, Eklöf O, Eriksson CG, Lins LE, Tidgren B, Winberg J. Development of hypertension and uraemia after pyelonephritis in childhood: 27 year follow up. BMJ 1989;299:703-6.
35. The Australia and New Zealand Dialysis and Transplant Registry. (http://www.anzdata.org.au.)
36. Sideras P, Smith CI. Molecular and cellular aspects of X-linked agammaglobulinemia. Adv Immunol 1995;59:135-223.
37. The International Nijmegen Breakage Syndrome Study Group. Nijmegen breakage syndrome. Arch Dis Child 2000;82:400-6.
38. Forbes GS, Hartman GW, Burke EC, Segura JW. Genitourinary involvement in chronic granulomatous disease of childhood. AJR Am J Roentgenol 1976;127:683-6.
39. Tullus K, Jacobson SH, Katouli M, Brauner A. Relative importance of eight virulence characteristics of pyelonephritogenic Escherichia coli strains assessed by multivariate statistical analysis. J Urol 1991;146:1153-5.
40. Jantunen ME, Siitonen A, Ala-Houhala M, et al. Predictive factors associated with significant urinary tract abnormalities in infants with pyelonephritis. Pediatr Infect Dis J 2001;20:597-601.
41. Ragnarsdóttir B, Fischer H, Godaly G, et al. TLR- and CXCR1-dependent innate immunity: insights into the genetics of urinary tract infections. Eur J Clin Invest 2008;38:Suppl 2:12-20.
42. Li YH, Yan ZQ, Brauner A, Tullus K. Activation of macrophage nuclear factor-kappa B and induction of inducible nitric oxide synthase by LPS. Respir Res 2002;3:23.
43. Tullus K, Escobar-Billing R, Fituri O, Lu Y, Brauner A. Soluble receptors to tumour necrosis factor and interleukin-6 in urine during acute pyelonephritis. Acta Paediatr 1997;86:1198-202.
44. Hussein A, Askar E, Elsaeid M, Schaefer F. Functional polymorphisms in transforming growth factor-beta-1 (TGFbeta-1) and vascular endothelial growth factor (VEGF) genes modify risk of renal parenchymal scarring following childhood urinary tract infection. Nephrol Dial Transplant 2010;25:779-85.
45. Faust WC, Diaz M, Pohl HG. Incidence of post-pyelonephritic renal scarring: a meta-analysis of the dimercapto-succinic acid literature. J Urol 2009;181:290-7.
46. Pohl HD, Rushton HG, Park JS, Chandra R, Majd M. Adjunctive oral corticosteroids reduce renal scarring: the piglet model of reflux and acute experimental pyelonephritis. J Urol 1999;162:815-20.
47. Sharifian M, Anvaripour N, Karimi A, et al. The role of dexamethasone on decreasing urinary cytokines in children with acute pyelonephritis. Pediatr Nephrol 2008;23:1511-6.
48. Doganis D, Siafas K, Mavrikou M, et al. Does early treatment of urinary tract infection prevent renal damage? Pediatrics 2007;120(4):e922-e928.
49. Bloomfield P, Hodson EM, Craig JC. Antibiotics for acute pyelonephritis in children. Cochrane Database Syst Rev 2005;CD003772.
50. Benador D, Neuhaus TJ, Papazyan JP, et al. Randomised controlled trial of three day versus 10 day intravenous antibiotics in acute pyelonephritis: effect on renal scarring. Arch Dis Child 2001;84:241-6.
51. Vilaichone A, Watana D, Chaiwatanarat T. Oral ceftibuten switch therapy for acute pyelonephritis in children. J Med Assoc Thai 2001;84:Suppl 1:S61-S67.
52. Levtchenko E, Lahy C, Levy J, Ham H, Piepsz A. Treatment of children with acute pyelonephritis: a prospective randomized study. Pediatr Nephrol 2001;16:878-84.
53. François P, Croizé J, Bost C, Wollschlager K. Comparative study of cefixime versus amoxicillin-clavulanic acid combination in the oral treatment of urinary tract infections in children. Arch Pediatr 1995;2:136-42. (In French.)
54. Montini G, Toffolo A, Zucchetta P, et al. Antibiotic treatment for pyelonephritis in children: multicentre randomised controlled non-inferiority trial. BMJ 2007;335:386.
55. Contopoulos-Ioannidis DG, Giotis ND, Baliatsa DV, Ioannidis JP. Extended-interval aminoglycoside administration for children: a meta-analysis. Pediatrics 2004;114(1):e111-e118.
56. Smellie JM, Katz G, Grüneberg RN. Controlled trial of prophylactic treatment in childhood urinary-tract infection. Lancet 1978;2:175-8.
57. Savage DC, Wilson MI, Ross EM, Fee WM. Asymptomatic bacteriuria in girl entrants to Dundee primary schools. Br Med J 1969;3:75-80.
58. Stansfeld JM. Duration of treatment for urinary tract infections in children. Br Med J 1975;3:65-6.
59. Williams GJ, Lee A, Craig JC. Long-term antibiotics for preventing recurrent urinary tract infection in children. Cochrane Database Syst Rev 2001;4:CD001534.
60. Garin EH, Olavarria F, Garcia Nieto V, Valenciano B, Campos A, Young L. Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. Pediatrics 2006;117:626-32.
61. Roussey-Kesler G, Gadjos V, Idres N, et al. Antibiotic prophylaxis for the prevention of recurrent urinary tract infection in children with low grade vesicoureteral reflux: results from a prospective randomized study. J Urol 2008;179:674-9.
62. Pennesi M, Travan L, Peratoner L, et al. Is antibiotic prophylaxis in children with vesicoureteral reflux effective in preventing pyelonephritis and renal scars? A randomized, controlled trial. Pediatrics 2008;121(6):e1489-e1494.
63. Montini G, Rigon L, Zucchetta P, et al. Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, noninferiority trial. Pediatrics 2008;122:1064-71.
64. Montini G, Hewitt I. Urinary tract in-

fections: to prophylaxis or not to prophylaxis? Pediatr Nephrol 2009;24:1605-9.
65. Craig JC, Simpson JM, Williams GJ, et al. Antibiotic prophylaxis and recurrent urinary tract infection in children. N Engl J Med 2009;361:1748-59. [Erratum, N Engl J Med 2010;362:1250.]
66. Brandström P, Esbjörner E, Herthelius M, Swerkersson S, Jodal U, Hansson S. The Swedish reflux trial in children. III. Urinary tract infection pattern. J Urol 2010;184:286-91.
67. Brandström P, Nevéus T, Sixt R, Stokland E, Jodal U, Hansson S. The Swedish reflux trial in children. IV. Renal damage. J Urol 2010;184:292-7.
68. Brandström P, Esbjörner E, Herthelius M, et al. The Swedish reflux trial in children. I. Study design and study population characteristics. J Urol 2010;184:274-9.
69. Koyle M. Editorial comment. J Urol 2010;184:285.
70. Dai B, Liu Y, Jia J, Mei C. Long-term antibiotics for the prevention of recurrent urinary tract infection in children: a systematic review and meta-analysis. Arch Dis Child 2010;95:499-508.
71. Keren R, Carpenter MA, Hoberman A, et al. Rationale and design issues of the Randomized Intervention for Children With Vesicoureteral Reflux (RIVUR) study. Pediatrics 2008;122:Suppl 5:S240-S250.
72. American Urological Association. Clinical guidelines. (http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines.cfm?sub=vur2010.)
73. Guay DR. Cranberry and urinary tract infections. Drugs 2009;69:775-807.
74. Jepson RG, Craig JC. Cranberries for preventing urinary tract infections. Cochrane Database Syst Rev 2008;1:CD001321.
75. Ferrara P, Romaniello L, Vitelli O, Gatto A, Serva M, Cataldi L. Cranberry juice for the prevention of recurrent urinary tract infections: a randomized controlled trial in children. Scand J Urol Nephrol 2009;43:1-5.
76. Wiswell TE, Smith FR, Bass JW. Decreased incidence of urinary tract infections in circumcised male infants. Pediatrics 1985;75:901-3.
77. Singh-Grewal D, Macdessi J, Craig J. Circumcision for the prevention of urinary tract infection in boys: a systematic review of randomised trials and observational studies. Arch Dis Child 2005;90:853-8.
78. Hoberman A, Charron M, Hickey RW, Baskin M, Kearney DH, Wald ER. Imaging studies after a first febrile urinary tract infection in young children. N Engl J Med 2003;348:195-202.
79. Lee MD, Lin CC, Huang FY, Tsai TC, Huang CT, Tsai JD. Screening young children with a first febrile urinary tract infection for high-grade vesicoureteral reflux with renal ultrasound scanning and technetium-99m-labeled dimercaptosuccinic acid scanning. J Pediatr 2009;154:797-802.
80. Lee HY, Soh BH, Hong CH, Kim MJ, Han SW. The efficacy of ultrasound and dimercaptosuccinic acid scan in predicting vesicoureteral reflux in children below the age of 2 years with their first febrile urinary tract infection. Pediatr Nephrol 2009;24:2009-13.
81. Zamir G, Sakran W, Horowitz Y, Koren A, Miron D. Urinary tract infection: is there a need for routine renal ultrasonography? Arch Dis Child 2004;89:466-8.
82. Montini G, Zucchetta P, Tomasi L, et al. Value of imaging studies after a first febrile urinary tract infection in young children: data from Italian renal infection study 1. Pediatrics 2009;123(2):e239-e246.
83. Bricker L, Garcia J, Henderson J, et al. Ultrasound screening in pregnancy: a systematic review of the clinical effectiveness, cost-effectiveness and women's views. Health Technol Assess 2000;4:1-193.
84. Bhide A, Sairam S, Farrugia MK, Boddy SA, Thilaganathan B. The sensitivity of antenatal ultrasound for predicting renal tract surgery in early childhood. Ultrasound Obstet Gynecol 2005;25:489-92.
85. Bosio M. Cystosonography with echocontrast: a new imaging modality to detect vesicoureteric reflux in children. Pediatr Radiol 1998;28:250-5.
86. Coulthard MG. Vesicoureteric reflux is not a benign condition. Pediatr Nephrol 2009;24:227-32.
87. Keren R. Imaging and treatment strategies for children after first urinary tract infection. Curr Opin Pediatr 2007;19:705-10.
88. Marks SD, Gordon I, Tullus K. Imaging in childhood urinary tract infections: time to reduce investigations. Pediatr Nephrol 2008;23:9-17.
89. Stefanidis CJ, Siomou E. Imaging strategies for vesicoureteral reflux diagnosis. Pediatr Nephrol 2007;22:937-47.
90. Smith T, Evans K, Lythgoe MF, Anderson PJ, Gordon I. Radiation dosimetry of technetium-99m-DMSA in children. J Nucl Med 1996;37:1336-42.
91. Hansson S, Dhamey M, Sigström O, et al. Dimercapto-succinic acid scintigraphy instead of voiding cystourethrography for infants with urinary tract infection. J Urol 2004;172:1071-4.
92. Preda I, Jodal U, Sixt R, Stokland E, Hansson S. Normal dimercaptosuccinic acid scintigraphy makes voiding cystourethrography unnecessary after urinary tract infection. J Pediatr 2007;151:581-4.
93. Fouzas S, Krikelli E, Vassilakos P, Gkentzi D, Papanastasiou DA, Salakos C. DMSA scan for revealing vesicoureteral reflux in young children with urinary tract infection. Pediatrics 2010;126(3):e513-e519.
94. Grattan-Smith JD, Little SB, Jones RA. Evaluation of reflux nephropathy, pyelonephritis and renal dysplasia. Pediatr Radiol 2008;38:Suppl 1:S83-S105.
95. Lim R. Vesicoureteral reflux and urinary tract infection: evolving practices and current controversies in pediatric imaging. AJR Am J Roentgenol 2009;192:1197-208.